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ABSTRACT

Aim: Clinical interpretation of B-Type Natriuretic Peptide (BNP) levels in hemodialysis patients (HD) for fluid management remains elusive.

Method: We conducted a retrospective observational monocentric study. We built a mathematical model to predict BNP levels, using multiple linear regressions. Fifteen clinical/biological associated with BNP variation were selected. A first cohort of 150 prevalent HD (from September 2015 to march 2016) was used to build several models. The best model proposed was internally validated in an independent cohort of 62 incidents HD (from March 2016 to September 2017).

Results: In cohort 1, mean BNP Level was 630±717 ng/ml. Cardiac disease (CD = Stable Coronary Artery Disease and/or Atrial Fibrillation) was present in 45% of patient. The final model includes: Age, systolic Blood Pressure (sBP), Albumin, CD, Normo-hydrated Weight (NHW) and the Fluid Overload (FO) assessed by bio-impedancemetry. The correlation between the measured and the predicted log-BNP was 0.567 and 0.543 in cohort-1 and 2 respectively. Age ($\beta=3.175e^{-2}$, $p<0.001$), CD ($\beta=5.243e^{-1}$, $p<0.001$) and FO ($\beta=1.227e^{-1}$, $p<0.001$) contribute the most significantly to the BNP level, respectively, but within a certain range. We observed a logistic relationship between BNP and age between 30 to 60 years, after which this relationship was lost. BNP level was inversely correlated with NHW independently of CD. Finally, our model allows us to predict the BNP level according to the FO.

Conclusion: We developed a mathematical model capable of predicting the BNP level in HD. Our results show the complex contribution of age, CD and FO on BNP level.

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INTRODUCTION

Biomarkers such as Natriuretic peptides (BNP, NT-proBNP) have been established as markers of mortality and cardiac events in Coronary Artery Disease (CAD) and Heart Failure (HF). [1] Both markers have been correlated with several cardiac parameters (Blood Pressure=BP, Left Ventricular Hypertrophy= LVH or LV systolic function) and non-cardiac parameters (Age, Gender, Diabetes mellitus or Body Mass Index=BMI). [2,3] Furthermore, some authors have also emphasized the utility of "BNP-targeted" heart-failure therapy in clinical practice. [4,5] In end stage renal disease (ESRD), especially in hemodialysis patients (HD), Cardiovascular Disease (CVD) is a burden and remains the first cause of mortality. [6] If both BNP an NT-Pro BNP are markers of cardiac events in ESRD, their use and interpretation (HD) still remains challenging.

BNP levels are often increased in HD. This can be partially explained by a decreased renal elimination but mainly by multiple factors both intrinsic (variability in measurement, type of BNP) and extrinsic related to patient comorbidity, including CVD or malnutrition. [7,8]. There is considerable variation in BNP levels over time and the cut-off values to define disease are not standardized across heterogeneous groups of patient populations. [9-14] Finally, the potential role BNP as a biomarker for fluid overload (FO) has been disappointing with discrepant results in small studies. [9–12] There is still debate as to whether this cardiac biomarker is more reflective of FO or intrinsic cardiac dysfunction in HD. Taken together, previous studies in HD have revealed that BNP levels can be influenced by many factors that may not have the same impact on BNP levels, and anticipation of a certain "targeted BNP level" to guide fluid-removal therapy is still missing.

When considering the interaction of different parameters for a specific outcome, mathematical modelling can be used as a robust method to understand and predict biological response. It has been widely used in pharmacodynamics to predict a drugs response, or in biology to predict cellular response. [13] We attempted to model the BNP level depending on several clinical and biological parameters in order to predict the "targeted" BNP for a given patient. The aim of the study was to; (1) assess to which extent each parameter will contribute to the BNP variation, and (2) to define a "targeted BNP" that could be used as a marker of fluid overload and to guide ultrafiltration. We built a mathematical model based on 6 clinical and biological variables that could be easily obtained at the patient bedside. We show for the first time the complex contribution of each variable in the modulation of BNP levels and the limitation in its interpretation such as age, CD and Dry Weight.

MATERIALS AND METHODS

The present study aimed to build a mathematical model, which enables accurate investigation of the relationship between BNP and clinical and biological parameters.

Patient population:

We initiated a single centre, observational, retrospective study of adult (>18 years old) HD. Inclusion criteria included; (1) Patient on hemodialysis > 6 months, (2) six consecutive monthly measures of BNP and haemoglobin, and (3) a minimum of two measures of the Normo-Hydrated Weight (NHW) by Body Composition Monitoring (BCM) during the 6 months observational period. Exclusion criteria included; (1) measure of BNP for a specific

cause (e.g acute congestive heart failure, acute coronary syndrome), and (2) patients with a pacemaker, implanted defibrillator or amputee because of the contraindication for BCM.

Two data sets were used: (1) Cohort 1 that included 150 (screened for eligibility from March 2015 to March 2016), to build the model and estimate its parameters; (2) Cohort 2 that included ~~62~~ ~~75~~ HD that started dialysis or were transferred to our centre from March 2016 to ~~March~~ December 2017. The latter was used to validate the proposed mathematical model.

We collected patient epidemiological and laboratory data using our Medical informatics record (Hemodial, PHP developpement, France).

In our centre, BNP measure is performed monthly with the routine blood test, since 2014. BNP level was performed before dialysis at the midweek session. Midweek measure was used to standardize results as it leads to a relative constant level of BNP. [14] BNP was measured by immunoassay on the Architect i2000 (Abbot Diagnostic). BNP levels <100 ng/L are considered normal in non-CKD, and the detection limits range from 2 to 5000 ng/L.

Albumin and C-reactive protein (CRP) were performed every 3 months. The presence of a stable CAD and/or Atrial Fibrillation (AF) defined cardiac disease (CD). Data for echocardiography were analysed when available. Echocardiography was performed on a non-dialysis day during the year of the study. Left Ventricular Mass Index (LVMI) and Left Ventricular Ejection Fraction (LVEF) were measured by standard techniques.

Estimation of Dry Weight and Fluid Overload

We used two different approaches to estimate the FO: (1) a "clinician approach" based on the dry weight (DW) estimated by the clinician. The clinician FO was defined by c-FO = pre-dialysis weight – DW; (2) a "bio-impedancemetry approach" that estimates the NHW. The bio-impedancemetry FO was defined by the FO = the predialysis weight – NHW. These 2

approaches were implemented into the models construction. The NWH was determined by BCM according to the manufacture's instructions (Fresenius®). Bio impedance analysis is a reliable, repetitive, and simple, technique to assess the fluid status of a dialysis patient. [15,16]

Modelling BNP level.

We performed a longitudinal study of all biological and clinical parameters measured monthly during 6 months**.** The asymmetrical distribution of BNP led us to consider a log-transformation for the statistical analyses, assuming a normal distribution for the log-BNP.

We first identified clinical and biological variables that have been shown to be associated with BNP variation in literature, We excluded cardiac parameters obtained form echocardiography (e.g. LVEF, LVMI) because data were not available for all patients at the beginning of the observational study

To generate the model, we used the following 15 variables of interest: Sex, Ethnicity, Age, Diabetes mellitus, Cardiac Disease (CD=1 if CAD and/or AF were present, CD=0 if not), post-dialytic Blood Pressure (BP), Hemoglobin (Hb), BNP, CRP, Albumin, Anti-hypertensive drugs (Beta-blocker, RAAS blocker, Calcium channel blocker), Clinical dry weight (DW) and c-FO, Normohydrated Weight (NHW) and FO.

Statistical analysis was performed using the computing environment R (R Development Core Team, 2017). Several linear models were fitted to the data, using the ln Function in R software. The best model was selected by minimizing the Bayesian Information Criteria (BIC). [17] Schwarz's BIC is a criterion for model selection among a finite set of models. If a model is estimated on a particular data set (training set), BIC score gives an estimate of the model performance on a new fresh data set (=testing set). The lower BIC score signals a better model. It is based, in part, on the likelihood function.

A test for interaction was performed for all variables. Benjamini-Hochberg procedure to was used properly take into account the multiple comparisons

The equation of the Final model is =

$$\log(BNP) = a0 + a1 * FO + a2/(0.02 + \exp(-Age/10)) + a3/(1e\text{-}05 + \exp(-sBP/15)) + a4 * NHW + a5 * CD + a6 * Alb$$

Coefficients a0 to a6 are listed in table 2.

Statistical analysis of demographic or biological characteristics.

All data with normal distribution were reported as a mean ± SD or a percentage. Comparisons between patients were performed using a non-parametric test (Whitney test) or chi-square test, and Fisher's exact test, as appropriate. Statistical significance was first established for a p value < 0.05.

RESULTS

Baseline Characteristic of the 2 data set.

Demographic and biological characteristics of cohort 1 and cohort 2 at the beginning of the study (=M0) are shown in **Table 1**. For cohort 1, the mean age was 67.1 years (range 21-93). Diabetes mellitus was found in 55/150 (36.6%) patients. Cardiac disease (CD), as defined by the presence of a stable CAD and/or AF was present in 63/150 (42%) patients. Twenty-six patients (17%) had a history of myocardial infarction.

The median dialysis vintage was 59 months (range 6-392). The majority of patients were on hemodiafiltration with a mean dialysis session time of 229±25 min. The mean Kt/v was

1.89±0.38. The c-FO was 2.65±1.33 kg and the FO, 1.8±1.88 kg. The sBP was 142/69 mmHg. Half of patients were taking anti-hypertensive drugs: 61 (40%) patients received beta-blockers, 70 (46%) received RAAS blockers. The mean hemoglobin was 11.2±1.3 g/dl. Mean BNP was 630 ± 717 ng/ml. Echocardiography data were available for 125/150 (83%) patients. The mean LVEF was 65±8% and the mean LVMI was 133±38 g/m^2.

Cohort 2 (=validation set) contained ~~62~~ 75 new incident patients **(Table 1)**. No statistically significant differences were observed between the learning and validation set, except for dialysis vintage, kt/v, c-FO, CRP, Prior myocardial infarction and the haemoglobin level. The latter reflects the presence of anemia usually observed at the beginning of dialysis. [18]

Construction and selection of a predictive model

We generated nine models that included the 15 clinical and biological variables **(see materials and methods**). We then selected among all the possible linear models the one that shows the best predictive performance for the BNP level, according to the Bayesian Information Criteria (BIC) (nine of the models are reported in **supplemental Table S1**). Briefly, the model with the lowest BIC is preferred. The best model obtained (=model m2) includes the following variables: Age, sBP, CD, Albumin, NHW and FO. The complete equation is detailed in the materiels and methods section. It should be noted that the model including FO estimated by bio-impedancemetry was considered slightly better than the one based on a "clinician-approach" for predicting the BNP level. Furthermore, diabetes mellitus, BMI and antihypertensive drugs that have been reported to influence BNP levels were not included from the final model. **Table 2** summarizes all the variables and their contribution for the m2 model.

The 3 variables that contribute the most significantly to the model (using the Relative important metrics method) were Age, FO and CD.

To exclude possible interaction between variable (e.g. effect modification by age upon CAD), we performed a test for interaction**. Supplementary table 2** summarize the results obtained with the 15 possible interactions (6 variables) are displayed in**).** None of theses models has a better BIC than the model without interaction, with adjusted p-values> 0.05.

Optimisation of the model

The correlation between the measured log-BNP and the predicted log-BNP was 0.567 in the learning set and was similar to the validation set (r=0.543). However, the multiple R-square, which determines the proportion of variability explained by the model, was low 0.32. This indicates that the 6 variables only explain 1/3 of the log-BNP variability ~~(multiple R-square = 0.32)~~

To improve the robustness of our model, we added the baseline values for the six variables at M0 as an additional explanatory variable in order to predict the BNP at further time points (M+1). The correlation between the measured log-BNP and the predicted log-BNP then increased to 0.794 (multiple R-square = 0.63) for the learning set and 0.759 for the validation set **(Figure 1).** It should be note that Age, CD and to a lesser extent NHY won't change between Mx and Mx+1. Thus the addition of BNP and sBP mainly explained the better correlation observed. These results emphasised the fact that a longitudinal screening of the BNP is mandatory.

Assessing the contribution of each variable.

Our model allows us to specifically assess the contribution of each variable for the BNP prediction, and to which extent they modulated BNP levels **(Figure 2-4);**. We defined a

standard hemodialysis patient, 67 years old, sBP 130/80 mmHg, FO=0, Albumin =36.5 g/l. By fixing values for 5 out of 6 variables, we could easily assess the effect of the remaining variable on the BNP level. For example, Figure 1 represents the predicted BNP according to age when sBP =130/80 mmH, FO=0 kg and albumin=36.5 g/l respectively.

We observed 3 different kinds of BNP modulation

(1) Effect of age and sBP mimic a dose-response curve (Sigmoid Curve) suggesting a minimal and maximal. Our model reveals BNP levels increase with age from 30 to 60 years old from 95 to 249 ng/ml (Fold Change FC = 2.83), before reaching a plateau **(Fig 2A)**. From 60 to 80 years, BNP levels only increase from 249 to 268 ng/ml. A similar effect was observed for the sBP **(Fig 2B)**. ~~For a sBP< 150 mmHg, we observed a small variation of BNP level from 251 to 287 ng/ml. However, BNP increases from 287 to 487 ng/ml if sBP rises to 200 mmHg (FC = 1.69).~~ The effect observed here was independent of the FO.

(2) A negative "linear effect" for albumin and NHW (**Figure 3**). For Each 10 g/l of albumin, BNP decrease with a FC=1.4 (**Figure 3A**). We observed that BNP levels also decrease with the NHW. ~~The predicted BNP was 360, 260 and 188 ng/ml for a NHW of 45, 70 and 100kg respectively without CD~~ (**Figure 3B**).

(3) A positive linear effect for CD and FO (**Figure 4**). CD was one of the top 3 variables that determined BNP levels with a FC of 1.69. Our model confirms also that Fluid Overload positively correlated with BNP independently of the CD. ~~Considering a 67 year old hemodialysis patient (sBP=130/80 mmHg), the predicted BNP for a FO of 0, 2.5 and 5 kg was 221, 304 and 418 ng/ml respectively; or 373, 514 and 707 ng/ml if CD is present~~.

Define the "right" BNP for a given patient.

Our model allows us to establish the "right" BNP is for a given patient. It could help clinician to target it for dry weight adjustment (**Table 3 and TableS3)** resume values of predicted-BNP

and the 95%IC according to different values for Age, Weight, FO and CD. We intentionally fixed values for Albumin and sBP to avoid too much information.

DISCUSSION

B-Type Natriuretic peptides have emerged as a useful biomarker in HF or CAD. In HD, BNP may be used as a sensitive marker of mortality but only in stable patients without HF, LVD or complex comorbidities. [19–21] However, interpretation of BNP levels is more complex due to the specific pathophysiology of ESRD and the presence of multiple comorbidities. All these confounding factors explain partially why studies fail to demonstrate the clinical use of BNP as a marker of fluid overload or to guide fluid removal. Anticipation of BNP values for a patient according to their clinical characteristics is lacking. In the present study, we built a mathematical model to predict the BNP in hemodialysis according to clinical and biological variables.

In our model, we identified the three variables that contribute the most significantly to BNP levels in dialysis patients: age, CD and FO. All these variables have been already associated with BNP level, but to which extent they contribute to it variation is new. ~~It is known that age is correlated with BNP levels in HF, CAD and dialysis. In our study population~~. For example, BNP increases with age in a linear manner up to 60 years. After this threshold, age does not influence BNP levels, suggesting that older patients will have similar baseline BNP levels. A similar effect was observed with sBP suggesting that the stretch of Left Ventricle induced by low sBP have minor effects on BNP modulation. However, it should be noted that the relation between blood pressure and BNP might be confounded by the use of medications (e.g RAAS or beta-blockers). [22] ~~Malnutrition has been associated with BNP levels in HD based on BCM~~

~~markers but not biomarkers such as albumin.~~ [8] ~~Here we emphasized the tight relationship between albumin and BNP. Albumin is not the optimal marker of malnutrition but its level is associated with poor outcome in HD.~~ [23] Our model also shows that BNP levels decrease according to a patients' weight, similarly to ~~These results correspond to~~ what has been described with BMI and BNP levels, ~~where lower circulating levels are observed in patients with a higher BMI~~ [24–27] . One possible explanation is that BNP clearance is increased due to the presence of the natriuretic peptide Clearance receptor (NPR-C) in adipose tissue. However, cardiac cachexia might also explain the higher BNP values in cases of low weight. This finding raises concern about the interpretation, predictive values and choice of cut-off values for Natriuretic peptides as in HF or reduced LVF. [24,26]

Our model emphasized that BNP levels are influenced by both intrinsic cardiac pathology HD and FO volume. In our 2 cohorts, even without HF, patients with a history of CAD or an AF had higher BNP levels compared to other HDs, independently of age or FO. This finding could reflect the presence of LVH observed in our patient. However, as HF measures (LVH, LVD) were excluded from the model, we could not definitively conclusion whether BNP is more reflective of FO or intrinsic cardiac dysfunction.

The potential role of BNP as a biomarker of volume excess is controversial [9–12] . Some authors have argued that BNP may only reflect FO in stable hemodialysis patient without underlying cardio-vascular disease. [11] Our model shows that even when considering various co-morbidities such as CD or diabetes mellitus, FO was one of most important predictors of BNP level. Our model allows us to anticipate the BNP level according to the patient's characteristics including the FO for a given dialysis-session. Comparison of the "predicted BNP" vs the "measured BNP" could give information about FO and help a clinician alter the dry weight adjustment. Estimation of the dry weight is critical is HD to avoid pulmonary

oedema or intradialytic Hypotension (IDH) that are both correlated with mortality. [28] Such "BNP-target" therapy should be assessed by a prospective study. Taken together, our findings demonstrated the complex modulation of BNP levels by each variable included in the model. This complexity may explain the seemingly conflicting results on BNP in dialysis patients.

When including the previous values M-1, our model only explains 2/3 for BNP variation. Several factors may explain this relative low correlation. First, the variability in the measure of variable such as BNP or sBP may weaken our model. BNP has a reduced half-life (20 min) as compare to NT-Pro-BNP (60-120 min), which will result in a higher variability of measure. We used a third generation kit for BNP measure that was different for previous reports. [8,9,11] Even if the performance of all Third generation kit showed similar result in HF or CAD with mild CKD (Stage 3-4), it is not known if their predictive values can be extrapolated to HD patient.

Secondly, the lack of inclusion of measure of LVH or LVD that are correlated well with BNP measure is also a major limitation. We also focused on clinical and biological variables that could be easily retrieve at bedside, which introduced bias. Finally, we acknowledged that the robustness of our model may be limited by it intrinsic properties. Several mathematical models (multiple linear regression, Polynomal regression or artificial network...) may be considered to predict a specific outcome. Each of them has their own advantage or limits.

Our study has however several limitations. First, it is retrospective mono-centre study without external validation. As mentioned earlier, variability in BNP measure and lack of echocardiographic measures weaken our results. The latter were excluded for 2 main reasons: 1/ data were not available for all patients at the beginning of the observational study and 2/

Echocardiography were also performed during the 6 months observational study at various time point by at least 5 different operators. The latter could also give rise to residual cofounding in our model.

Finally we did not perform quantification of diuresis in our patients because of the retrospective analysis, and the absence of consensus for diuresis estimation in hemodialysis. Notwithstanding, our study has however several strengths including, the number of patients (N=150) and data implemented in the model (Number of observation = 840), and the validation of the model in an independent cohort.

To conclude, we built a mathematical model based on 6 parameters, which allows the prediction of the BNP level in hemodialysis patient for clinical practice. Our study emphasized the fact that the BNP level for a given hemodialysis patient, is influenced by 3 main factors: Age, CD and FO. Whilst our model could be currently used for dry weight adjustment and prevent IDH, a further prospective study is required.

Contribution

MT and ML contributed to the conception of the study. MT, ALL, CM and KM collected the data. MT and ML analysed the data. MT drafted the manuscript. MT, ML, TP and CR contributed to writing the article.

Conflict-of-interest disclosure: The authors declare no competing financial interest.

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LEGEND

Figure 1

Correlation between predicted BNP and measured BNP for the learning set (**A**), and the validation set (**B**).

Figure 2

Predicted BNP according to Age (**A**), and systemic Blood Pressure, mmHg (**sBP**). Values were calculated for a 67 year old male patient, sBP 130/80 mmHg, Albumin 36g/l, NHW = 67 kg and FO = 2 kg. Blue and red curves indicate the absence and presence of a Cardiac disease (CD) respectively.

Figure 3

Predicted BNP according to NormoHydrated Weight (NHW, kg) (**A**), and Albumin (Alb, g/l) (**B**). Values were calculated for a 67 year old male patient, sBP 130/80 mmHg, Albumin 36g/l, NHW = 67 kg and FO = 2 kg. Blue and red curves indicate the absence and presence of a Cardiac disease (CD) respectively.

Figure 4

Predicted BNP according to the Fluid Overload (FO): Values were calculated for a 67 year old male patient, sBP 130/80 mmHg, Albumin 36g/l, NHW = 70 kg. Blue and red curves indicate the absence and presence of a Cardiac disease (CD).

	Cohort 1 N=150	Cohort 2 N=75	P-values
Age (mean, range)	67.1 (21-93)	64.1 (19-97)	0.208
Sex (F/M)	61/89	29/46	0.885
Ethnicity (N)			
- Caucasian	76	41	0.671
- Maghreb	41	4	0.135
- Afro-American	22	12	0.844
- Chinese	6	5	0.512
- Indian	5	4	0.485
Nephropathy (N%)			
- Glomerular	83 (55.3%)	38 (51%)	0.571
* Diabetes	42 (28%)	25 (33.3%)	0.441
* Others	41 (27.3%)	13 (17.3%)	0.135
- Vascular	35 (23.3%)	14 (18.6%)	0.494
- TIN	17 (11.3%)	4 (5.3%)	0.223
- APKD	9 (0.6%)	4 (5.3%)	1
- Unknown	6 (0.04%)	15 (20%)	< 0.001
Comorbidities			
- Diabetes	55 (36.6%)	22 (29.3%)	0.299
- BMI (kg/m$^{2)}$	25.9±4.9	24.9±4.5	0.381
Cardiovascular disease	63 (42%)	30 (40%)	0.886
CAD	43 (29%)	17 (22.6%)	0.424
Atrial Fibrillation	33 (22%)	16 (21.3%)	1
Prior Myocardial Infarction	26 (17%)	4 (5.3%)	0.012
Cardiac Surgery	10 (7%)	4 (5.3%)	0.778
Valvular disease	16 (11%)	15 (20%)	1
Echocardiography			
Available (N)	125/150 (83%)	56/75 (75%)	
LVEF (%)	65± 8	62±13	0.412
LVMI (g/m^2)	133±38	132±45	0.762
Treatment			
B-Blockers	61 (40%)	41 (55%)	0.064
RAAS Blockers	70 (46%)	38 (51%)	0.575
Calcium Channel Blocker	42 (28%)	26 (34%)	0.335
RTT			
- Time (months, median-range)	59 (6-392)	16 (6-97)	<0.0001
- Type: HD/HDF	3/147	12/63	<0.0001
- Kt/v	1.89±0.38	1.38±0.43	<0.0001
- Dialysis time (min)	229±25	224±61	<0.0001

	Cohort 1 N=150	**Cohort 2 N=75**	**P-values**
BNP ng/ml (Mean, SD**)**	630±717	563±592	0.770
Hemoglobin g/dl (Mean, SD)	11.2 ±1.3	10.5±1.6	<0.0001
Blood Pressure (mmHg) Systolic Diastolic	 142±27 69±15	 144.3 ± 27 71.1 ± 18.2	 0.432 0.705
Fluid estimation (kg) c-FO FO (impendancemetry)	 2.65 ±1.33 1.8 ± 1.88	 2.07±1.57 1.52 ± 2.1	 0.002 0.329
Patient weight (kg) Dry Weight NHW	 67.5 (38.5-113) 68.3 (37-113)	 69.9 (41-123**)** 70.1 (39.7-122.2)	 0.690 0.530
CRP mg/l (mean, SD)	9.3 ±10.2	8.2±9.5	0.016
Albumin g/dl (Mean, SD)	36.5 ± 3.9	35.2±6.5	0.074

Table I: Demographic and biological characteristics of the learning and validation set at M0

Abbreviation: F: female; M: male; TIN: Tubulo-interstital Nephropathy; APKD: Autosomic dominant Adult Polycystic Kidney Disease; BMI: Body Mass Index; cFO: clinical Fluid Overload; FO: Fluid Overload assessed by bioimpendancemetry; RAAS Blockers: Renin-angiotensin-aldosterone System blockers; CRP: C-reactive Protein; RRT: Renal Replacement Therapy; HD: Hemodialysis; HDF: Hemodiafiltration; NHW: NormoHydrated Weight. LFEV: Left Ventricular Ejection Fraction; LVMI: Left Ventricular Masse Index, Kt/V : K= Dialyzer clearance, T= Time, V = Volume of water a patient's body contains.

	Coefficient	SD	T value	P-value	lmg
Intercept (=a0)	$5.610e^{-00}$	$5.33e^{-3}$	11.064	$<2e^{-16}$	0.32813
Age (=a2)	3.175e-2	4.719e-3	6.728	5.17e-11	0.32813
CD (=a5)	5.243e-1	9.549e-2	5.49	6.67e-8	0.21161
FO (=a1)	1.227e-1	2.59e-2	4.926	1.17e-7	0.15700
sBP (=a3)	7.79e-6	1.954e-6	3.986	7.83e-5	0.10271
Albumin (=a6)	-3.4e-2	1.152e-3	-2.954	3.29e-3	0.09544
NHW (=a4)	-1.182e-2	2.931e-3	-4.03	6.5e-5	0.08406

Table II : Variables included in the final model

Abbreviation: FO: Fluid Overload assessed by Bioimpedancemetry; sBP: systolic Blood Pressure; CD: Cardiovascular disease; NHW: NormoHydrated Weight, lmg: relative important metric.

Model	Variables	BIC
m1	Age, sBP, CD, **NHW, FO**	1304.2
m2	m1+ Albumin	1301.6
m3	Age, sBP, CD, **DW, c-FO**	1304.8
m4	Age, sBP, CD, BMI, FO, Albumin	1304.9
m5	m2 + CRP	1306.7
m6	m2 + anti hypertensive drugs	1316.9
m7	m2 + diabetes mellitus	1306.8
m8	m2 + sex	1307.7
m9	m2 + ethnies	1319.0

Supplemental Table 1 : Model list

Abbreviations: BIC: Bayesian information criterion; sBP: systolic Blood Pressure; Hb: hemoglobin, CD: Cardiac disease; NHW: Normo-Hydrated Weight; FO: Fluid Overload assessed by bio-impedancemetry; CRP: C reactive protein; DW: Clinician Dry Weight; c-FO : clinical Fluid overload; BMI: Body mass Index.

Variable 1	Variable 2	BIC	p-value	p-value adjusted
sBP	Albumin	1301.9	0.016	0.139
sBP	Age	1302.4	0.022	0.139
FO	Age	1302.9	0.030	0.139
FO	NHW	1303.7	0.046	0.139
NHW	Albumin	1303.7	0.046	0.139
FO	CD	1304.5	0.077	0.190
NHW	CD	1304.8	0.089	0.190
sBP	CD	1305.0	0.101	0.190
NHW	Age	1305.4	0.135	0.225
Albumin	CD	1306.0	0.200	0.299
Age	CD	1306.6	0.294	0.401
Age	Albumin	1307.3	0.520	0.627
sBP	NHW	1307.3	0.55	0.627
FO	sBP	1307.4	0.585	0.627
FO	Albumin	1307.6	0.782	0.782

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Supplementary Table 2: test of interaction for all variables

Abbreviations: BIC: Bayesian information criterion; sBP: systolic Blood Pressure; CD: Cardiac disease; NHW: Normo-Hydrated Weight; FO: Fluid Overload assessed by bio-impedancemetry.

Benjamini-Hochberg multiple comparison test was used for the p-value adjusted.